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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/758,957	01/11/2001	Robert N. Hanson	ZAA-011.01	9648

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/758,957	HANSON ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,18,19 and 55-60* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 55-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed March 1, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 15, 17-19 and 55-60 were pending. Applicants amended claims 15, 18-19 and canceled claim 17. Therefore, claims 15, 18-19 and 55-60 are pending.

4. Newly amended claims 18-19 are now drawn to methods of use, which read on the invention of Group IV or represent separate and patentably distinct invention for the same reasons outlined in the previous restriction requirement (e.g., see Paper No. 6, paragraphs 1 and 7-8). This Group was not elected for examination and therefore claims 18-19 are also withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

5. Therefore, claims 15 and 55-60 are examined on the merits in this action.

Withdrawn Objections/Rejections

6. The objections to claims 17-19 are withdrawn in view of applicant's amendments thereto and/or cancellation of claims. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

7. Claims 15 and 55-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not provide support for the invention as now claimed. Applicant's amendment asserts that "the specification gives ample support for the claimed compounds" (After Final, page 5); however, the Response does not point to any specific support for the newly proposed generic structures (i.e. formula (**II**)) and the generic structure does not appear anywhere in the instant specification (Applicants also do not show where support can be found in their 3/1/2004 Response). The specification as originally filed includes only ***two*** specific structures that would read on the presently claimed generic (i.e. Figure 9). This is deemed to be insufficient support for the newly recited generic that encompasses a wide variety of compounds outside of those presented in Figure 9. For example, consider just the members of the proposed Markush group for R_1. The two compounds of Figure 9 contain a -CO_2H group at this position *only*. So, there is only support for the proposed $R_1 = -CO_2R_4$ where $R_4 = H$ i.e., Applicants only provide support for $R_1 = -CO_2H$. However, R_1 also recites "-

$CO_2N(R_4)_2$" and R_4 also recites alkyl. The -CO_2(H) is *not* sufficient support for -$CO_2N(alkyl)_2$ or -CO_2(alkyl). For example, Hydrogen and alkyl groups are NOT bioisosteres (i.e., interchangeable) because they have different size, shape, electronic distribution, lipid solubility, water solubility, pK_a, chemical reactivity, and hydrogen bonding (e.g., see Silverman et al., pages 19-23). For example, an alkyl group attached to a carboxylic acid (i.e., the "R" portion of the -CO_2R ester group) cannot undergo hydrogen bonding like the hydrogen atom that is attached to a carboxylic acid can (i.e., the "H" portion of the -CO_2H acid group). In addition, the alkyl groups are larger than the hydrogen and more lipophilic and have much higher pKa values. Thus, Applicants' example of a hydrogen atom at the R_4 position does not provide support for an alkyl group at this same position because these groups would have significantly different physiochemical properties (as mentioned above) and thus do not have similar structural features and/or reactivity. Moreover, the -F atoms in the para positions of the GBR 12935 phenyl rings do not supply support for H, F, Cl, Br or I in those positions. In addition, the -H in the ortho and meta positions of the GBR 12935 phenyl rings do not supply support for H, F, Cl, Br or I in those positions.

Response

8. Applicant's arguments directed to the above New Matter rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that "disclosure of a carboxylic acid substituent e.g., R_1 = $-CO_2H$, provides sufficient support for the fact that the substituent also might be an ester or amide group" because of "their similar structural features and reactivity" and cites Organic Chemistry 2nd Ed by Bruice in support of this position (e.g., see 3/1/2004 Response, page 5, paragraph 1).

[2] Applicants argue that with respect to the R_2 and R_3 positions, "the fluoride substituent provides sufficient support for the fact that the substituent may be chloride, bromide, or iodide because all these groups are halogens" (e.g., 3/1/2004 Response, page 5, paragraph 2).

This is not found persuasive for the following reasons:

[1] First, the Examiner contends that Applicants arguments are not commensurate in scope with the claims. For example, Applicants state that a carboxylic acid substituent provides support for an "amide" group, but the Examiner notes that no amide groups are currently being claimed (i.e., Applicants are claiming a "$-CO_2N$" group NOT a "-CON" group as alleged). Thus, Applicants arguments are moot with respect to the $-CO_2N$ group (i.e., a carbamate group) because Applicants' cited reference (i.e., Bruice) does not mention "carbamate" in the list of carboxylic acid derivatives (e.g., see 3/1/2004 Response, page 5, paragraph 1, "acyl halides, acid anhydrides, esters, and amides are all called carboxylic acid derivatives"). Furthermore, the Examiner notes that carbamates are generally considered to be derivatives of "carbonic acids", which have very different properties than "carboxylic acids" because, for example, they are unstable (i.e., they decompose spontaneously into carbon dioxide and water) (e.g., see Solomons, T. W. G. Organic Chemistry Fifth Edition. New York: John Wiley and Sons. 1992, pages 796-797).

Second, the Examiner contends even if *assuming arguendo* Applicants' -CO_2N group was to somehow read on an "amide" group, a hydrogen atom in the R_4 position is NOT bioisosteric (i.e., interchangeable) with an alkyl group at this same position (e.g., see Silverman, R. B. The Organic Chemistry of Drug Design and Drug Action. New York: Academic Press, Inc. 1992, pages 19-23, especially page 19, "Bioisosteres are substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties"; also note that hydrogen and alkyl are not listed together on an isosteric or bioisosteric table). Hydrogen and alkyl groups are NOT bioisosteres because they have different size, shape, electronic distribution, lipid solubility, water solubility, pK_a, chemical reactivity, and hydrogen bonding (e.g., see Silverman et al., page 21 wherein many important physiochemical properties that effect a molecules biological activity are listed). For example, an alkyl group attached to a carboxylic acid (i.e., the "R" portion of the -CO_2R ester group) cannot form a hydrogen bond because the alkyl group contains only C-H bonds that are non-polar whereas a hydrogen atom that is attached to a carboxylic acid (i.e., the "H" portion of the -CO_2H acid group) can form a hydrogen bond because the O-H bond is polar (see Solomons, page 77, "Very strong dipole-dipole attractions occur between hydrogen atoms bonded to small, strongly electronegative atoms (O, N, or F) and nonbonding electron pairs ... Molecules of dimethyl ether [and also alkyl group which also possess only C-H bonds], because they lack a hydrogen atom attached to a strongly electronegative atom, cannot form strong hydrogen bonds"). In addition, the alkyl groups are larger than the hydrogen, more lipophilic and have much higher pK_a values (e.g., see Solomons, page 94 and 441 and compare also Table 18.2 to Table 18.4). Thus, Applicants' example of a hydrogen atom at the R_4 position does not provide support for an alkyl group at this

same position because these groups would have significantly different physiochemical properties (as mentioned above) and thus do not have similar structural features and/or reactivity as Applicants contend.

[2] First, the Examiner contends that Applicants arguments are not commensurate in scope with the claims because no "F" substituents are found at the *ortho* and *meta* positions of the phenyl rings (e.g., see figure 9 of specification) and, as a result, there is no "F" substituent to provide support for the other halogens.

Second, with respect to the "F" substituents at the *para* position of the phenyl rings (e.g., see figure 9 of specification) the Examiner contends that Applicants have not provided any "identifying" language that would encompass the claimed genus (e.g., Applicants do not state in the specification that a "halogen" can be substituted at the *para* position). For example, in *In re Grimme, Keil, and Schmitz* 124 USPQ 499 (CCPA 1960) the Court held that naming one member of a chemical genus (i.e., a single species) is not, in itself, proper basis for a claim to an entire chemical genus unless the genus is sufficiently identified in the application by other appropriate language (e.g., see In re Grimme, Keil and Schmitz 124 USPQ 499, 501) ("On the other hand, in the case of a small and closely related group such as the halogens, ***the naming of the group*** should ordinarily be sufficient since nothing of consequence would be added by also naming each of the well known members of the group"). Here, Applicants failed to "name the group" and thus do not provide any "identifying" language (e.g., halogen) that would support the claimed genus. Therefore, the disclosure of a single species (i.e., the "F" atom) in the *para* position of the phenyl rings fails to satisfy the test set forth in *In re Grimme, Keil and Schmitz* because Applicants have not provided any "identifying" language and, as mentioned above, a

single species is not, in itself, a proper basis for a claim to an entire chemical genus unless such identifying language is set forth in the specification.

Accordingly, the New Matter rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 21, 2004

BENNETT CELSA
PRIMARY EXAMINER